

## **REMARKS**

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 67-93 are in this case. Please cancel claim 74. Claim 72 has been withdrawn from consideration. Claims 67-71 and 73-93 have been rejected under 35 USC § 112. Claim 91 has been objected to. Claims 67-73 and 75-93 have been amended. Claims 67-73 and 75-93 remain in this application.

The claims before the Examiner are directed towards a method and device for the diagnosis of a medical condition related to epilepsy

### **In the specification**

1. Applicant has corrected the claims as requested by the Examiner, namely by amending the numbering of the claims as well as the amendment of the numbering of found within the dependent claims.
2. The Examiner has found a large blank space on page 18 of the instant specification. Applicant confirms that this is indeed a blank space and that no text has been lost. Applicant has attached hereto a replacement page 18 where the large blank space has been crossed through.
3. On page 19 line 7 of the instant specification the Examiner has found an open parenthesis and on page 19 line 14 a missing period. Applicant has amended these unintentional typographic errors by erasing the extraneous parenthesis on page 19 line 7 and by adding a period to the end of page 19 line 14. In the same paragraph, Applicant has seen that ETS was spelled Ets. Applicant has capitalized ETS and added, in parentheses, the clarification that the referred to moiety is ethosuximide to increase legibility.
4. Examiner has requested that format of sub-sub-subnumbers found in claim 91 be changed to prevent confusion with subnumbers. Applicant has amended claim 91. Claim subnumbers are selected from letters a, b, c. Claim sub-subnumbers are selected from small roman numerals i, ii, iii. Claim 91 sub-sub-subnumbers are

selected from italic *ii.a*, *ii.b* and *ii.c* indicating the dependence of the limitations of claim 91 on claim 89.

### **35 USC § 112 Rejections**

Claims 67-71 and 73-93 are rejected under USC 112 as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains

5. Claims 67-71, 73 and 78-94 are directed to a method for diagnosing a medical condition related to epilepsy, which comprises measuring a concentration of at least two kynurenine metabolites.

In paragraph 7 of the instant Office Action, the Examiner finds that that the instant specification does not provide any guidance or working examples on how to diagnose a medical condition related to epilepsy by the claimed method or how to use the claimed system. The Examiner's rejection is respectfully traversed.

As the Examiner states the present is unique in the art in demonstrating or suggesting that a medical condition can be diagnosed based on measuring and comparing concentrations of kynurenine metabolites. In fact, diagnosis of a number of diseases, especially genetic diseases, such as hypophosphatasia, phenylketonuria, histidinemia, homocysteinuria, maple syrup urine disease is based on identifying an altered amount of some or the other metabolite. Screening-tests for metabolic defects are based on detection of altered concentrations of different metabolites in the blood, urine, or other fluids of patients, see for example Menkes, J. H. *Textbook of Child Neurology*, 5th Ed. 1995 Williams & Wilkins, Baltimore MD (ISBN 0-683-05920-3).

Applicant would like to bring the article Heyes *et al*, *Epilepsia* 1994, 35, 251-257 to the attention of the Examiner, specifically page 253, paragraph beginning at the bottom of the first column. Therein Heyes *et al* demonstrates a relationship between kynurenine concentrations in spinal fluid and serum and epilepsy. Despite approaching the teachings of the present invention, on page 255, column 2, lines 43 to 48, Heyes states "...general disturbances in kynurenine pathway metabolite levels occur in patients with CPS. The changes ... may be related more to confounding variables... than to etiological processes." and thus teaches away from the utility of the relationship.

Other references that note a relationship between kynurenines and epilepsy without recognizing the diagnostic potential therein are: Yamatomo *Brain Dev.* **1995**, 17, 327-329; Milanovic *Advances in Experimental Medicine and Biology* **1996**, 398, 103-106 and Pellicciari *J. Med. Chem.* **1994**, 37, 647-655 as well as the prior art cited on pages 4 and 5 of the instant application.

Further, the Examiner finds that independent claim 67 is too broad due to the breadth of limitation "d. diagnosing a medical condition based on results of said comparing." As often done when allowing a patent, an inventor is given broad protection for the teachings of an invention in an open field to avoid that others, upon seeing the success of the teachings of an inventor, unfairly apply the knowledge gleaned therein for their own profit. Thus Applicant sought protection for the general "medical condition" knowing that in the future, neurological diseases will be identified to be related to epilepsy in influencing the kynurenine metabolism and thus subject to diagnosis according to the teachings of the present invention. For example, ADHD is considered by some experts to be an epilepsy related disorder (*vide infra*).

Although continuing to traverse the Examiner's opinion that limitation d of claim 67 is too broad Applicant has, in order to expedite prosecution of the instant application, chosen to add to independent claim 67 the limitations of dependent claim 74 "wherein said medical condition is related to epilepsy." Further, claims 75 and 76, heretofore dependent on claim 74 have been amended to depend from claim 67.

In the specification of the instant application, Applicant has demonstrated the utility and potential in diagnosis of epilepsy and predisposition to epilepsy of the present invention. Diagnosis is not aimed at the etiology of any specific form of epilepsy, but rather at the specific dysfunction of the kynurenine pathway that is characteristic of epilepsy and of a predisposition to epilepsy in general. Also, control of AED treatment can be realized by monitoring AED-induced kynurenine level alterations using the teachings of the present invention.

Applicant has performed clinical studies indicating that patients suffering from prevalent forms of epilepsy, independently of the specific form of the disease, are distinguishable from healthy individuals by characteristic changes of the concentrations of neuroprotective and neurotoxic kynurenine metabolites. The samples obtained from patients with the following forms types of epilepsy were analyzed:

Grand mal-generalized tonic-clonic seizures;

Petit mal-absence seizures;  
Complex partial seizures;  
Simple partial seizures; and  
Repeated febrile convulsions as condition of epilepsy predisposition.

Additionally, recently Applicant has shown that Attention deficit hyperactive disorders (ADHD) is a genetic disorder related to epilepsy (Matsuura M. *et al Biol. Psychiatry* **1993**, Jul 1-15; 34(1-2): pp. 59-65. and Suffin S.C., Emory WH, *Clin. Electroencephalography* **1995** Apr: 26(2), pp. 76-83.) is also characterized by disordered tryptophan metabolism, including alterations in vitamin B6 dependent kynurenine pathway. Thus, the method of the present invention is also applicable for the diagnosis of ADHD.

Further, the Examiner states that the *"instant specification fails to provide guidance ...how one could obtain any sample from a subject, measure concentration of kynurenine metabolites and after comparing the results with control values or after establishing a ratio between said metabolite concentrations, provide a diagnosis"*. The Examiner's statement is respectfully traversed. The method of obtaining a sample from a subject, be it blood, urine, spinal fluid or other fluid or tissue is clear to one skilled in the art, just as is the quantification of kynurenine metabolites within such samples. Similarly, methods of determining reference values from a sufficiently large "normal" population are normal laboratory procedure and needs not be detailed. For example, the reference values of some kynurenines characteristic of normal population can be found in Geigy Scientific Tables, Ciba-Geigy, 1981. Other authors (including those mentioned hereinabove) have measured kynurenines both in individuals suffering from epilepsy and in healthy individuals using HPLC (as did Applicant) or other applicable methods.

6. Amended claim 67 and dependent claims 75, 76 and 77 are directed to a method for diagnosing a medical condition, which is related to epilepsy.

In paragraph 8 of the instant Office Action, the Examiner finds that that the instant specification fails to describe how predictive the animal model is for specific forms of epilepsy. The Examiner's rejection is respectfully traversed. In the art it is accepted that animal models be used in pre-clinical studies for those clinical studies which have an accepted corresponding animal model. The validity of these pre-

clinical animal studies is not doubted. It is not generally required to wait until tests in humans show results to file for patent protection as the time and expense is much too significant and such a requirement would stifle innovation.

Animal models of genetic epilepsy are known to be highly predictive. Specifically, one model used by Applicant, epilepsy-prone animals, was firstly described in 1924 in Pavlov's laboratory and later intensively studied from the 1930s and 1940s. Since then, hundreds of papers concerning the pathogenesis of epilepsy and development of anti-epileptic drugs were carried out on animal models of epilepsy. NIH anticonvulsant screening project uses only animal models of epilepsy, including those used in preparing the instant application, for screening anti-epileptic drugs. Important references were recently collected in the paper published by J.P. Stables and H. J Kupferber: "The NIH Anticonvulsant Drug Development (ADD) Program: preclinical anticonvulsant screening project" in "Molecular and cellular targets for anti-epileptic drugs", 1997. Thus, the predictivity of these animal models of genetic epilepsy is generally accepted by those skilled in the art. It is important to note that based on detection of an error of metabolism detected in animal models of genetic epilepsy and then clinically confirmed in epileptic patients, Applicant has developed a novel family of anti-epileptic drugs having a unique binary structure, described in US Patent Application 60 / 300,818 filed on June 26 2001.

The animal used in preparation of the instant application, seizure-naïve genetically epilepsy-prone (EP) rats, is the model of genetic predisposition to epilepsy. These animals do not have spontaneous convulsions, but display generalized epileptic tonic-clonic attacks under the precipitating factor of intense sound (90-105dB), that does not induce epileptic attacks in control epilepsy-resistant (ER) rats. As shown in the examples of the instant application, the imbalance between the concentrations of neuroprotective and neurotoxic kynurenines in the blood of these seizure-naïve animals was similar to the results obtained in FC patients considered as predisposed to epilepsy (Febrile Convulsive FC group).

The second animal model used by Applicant is a rat with spontaneous non-convulsive absence seizures (GAER) developed by Professor Marescaux in Strasbourg. This model is considered as a unique model of human absence epilepsy. EEG patterns of these animals are characterized by spontaneous spike-wave complexes (7-8/sec) and are accepted as almost exact analog of human absence EEG. The model rat is used by, *inter alia*, pharmaceutical companies to evaluate the

effectiveness of anti-epileptic drugs aimed specifically at the treatment of absence form epilepsy. Hence, Applicant believes the Examiner's objections that "*The instant specification fails to describe how predictive the animal model of rat epilepsy would be for, for example, human patients suffering from seizure disorders or from which particular forms of epilepsy*" is overcome, as well as the objection "*no evidence of records that the claimed method for diagnosis of epilepsy, or predisposition to epilepsy, based on discovered difference in concentration of kynurenine metabolites of genetically epileptic rats, can be extrapolated and successfully practiced on human subjects suffering from epilepsy regardless of particular type or origin of the disorder*".

In fact, Applicant is describing the use of biomarkers for epilepsy and related medical conditions. Search for biomarkers is a target of modern diagnostics. At present, biomarkers allow diagnosing of diseases, and differentiating people predisposed to the disease but clinically healthy, from those who do not have biochemical signs of predisposition. Also biomarkers are often used for monitoring treatments of diseases. The Examiner casts doubt on the possibility that a common biochemical marker be common for different types of a disease and cites the 1987 edition of the Merck Manual. In the 1987 edition of the Merck Manual (p.1387, first paragraph), it is indicated that genetic metabolic disorders were long ago assumed as a reason for epilepsy origin: "*...it is more likely that unexplained, predominantly inherited metabolic abnormalities underlie most idiopathic cases*". The instant application is focused at the inherited metabolic abnormalities, which underlie epilepsy as a genetic seizure disorder, and at the detection of biomarkers specific for this inborn error of metabolism. The biomarkers applicable to epilepsy were not even discussed in 1987.

Applicant traverses the opinion of the Examiner found in paragraph 8 of the instant Office Action "*different cases of epilepsy or seizures have different etiology, origin and development*". This opinion, although not uncommon, is unsubstantiated and there is no evidence supporting it. Although different precipitating factors may induce different forms of epilepsy, Applicant believes that a common inborn error of metabolism may underlie the enhanced convulsibility characteristic of all different forms of epilepsy and related medical conditions. Applicant believes that an inborn error in vitamin B6 metabolism underlies genetically enhanced convulsibility and can be revealed by detection of altered concentrations of the metabolites, which are

formed in the course of biochemical pyridoxal phosphate (vitamin B6)-dependent reactions. Pyridoxal phosphate is a coenzyme for numerous essential metabolic reactions within the nervous system. Previous publications of one of Applicants and her collaborators have shown that vitamin B6-dependent biochemical pathways are disordered in genetic epilepsy. ((a) Dolina, S. and Kozak, H. "Is B6 dependency an essential factor of genetic predisposition to epilepsy?" in 17th Epilepsy International Congress Book of Abstracts, Jerusalem 1987:34. (b) Dolina, S. "Is pyridoxine dependency an inborn error of metabolism triggering an enhanced convulsibility in different animal models of genetic epilepsy?" a commentary in *Neurosci. (Kobe)* 1992; 18 supplement 2, pp. 153-162. (c) Dolina, S.; Peeling, J.; Sutherland, G.; Pillay, N.; and Greenberg, A. "Effect of sustained pyridoxine treatment on seizure susceptibility and regional brain amino acid levels in genetically epilepsy-prone BALB/c mice." *Epilepsia* 1993, 34, pp. 33-42.

Therefore, Applicant has chosen the vitamin B6-dependent kynurenine pathway of tryptophan degradation (the pathway that includes the enzymatic reactions most sensitive to vitamin B6 supply) in a search for biomarkers indicative of genetically enhanced seizure susceptibility. Since filing of the instant application, this hypothesis has been confirmed by results obtained during clinical trial of more than 150 blood-samples and more than 300 urine-samples taken from epileptic patients (mostly children) with different forms of epilepsy including:

- grand mal-generalized tonic-clonic seizures;
- petit mal-absence seizures;
- complex partial seizures;
- simple partial seizures; and
- febrile convulsions as condition of epilepsy predisposition.

It is important to note that the samples were taken at different stage of the disease from the first epileptic attack and the beginning of AED treatment up to cancellation of AED treatment. The results obtained have shown, for example, that the method of the present invention has a predictive value in cases of urgent AED treatment of epileptic attack clusters or under threat of relapse resulting from AED treatment cancellation.

Further, as concerns the results of a predisposition to epilepsy. The Examiner notes that there is no data confirming how many children diagnosed as having a

predisposition to epilepsy eventually developed epilepsy. Considering that such an experiment would require at least ten years to perform, more likely twenty, it is an unfair requirement. It is not necessary to present such data. Predisposition to any disease does not mean that all predisposed individuals, or that even a statistically significant number of them, will develop some disease within 20 years. Predisposed individuals are a group of high risk. Being first or second-degree relatives of epileptic patients, these individuals have genetically affected metabolism as a background for future disorder. Having this specifically affected metabolism, they are more sensitive to the disease and may develop disease under precipitating factors, which will not induce a disease in individuals without signs of predisposition. A method identifying individuals predisposed to epilepsy will allow a prophylactic approach.

7. In paragraph 10 of the instant Office Action, the Examiner finds that claims 67 and 89 are indefinite because of the recitation of "corresponding reference concentrations". It is not clear to the Examiner how reference values can be established before diagnosis. The Examiner's rejection is respectfully traversed. In the art, methods of establishing reference concentrations are well known. As has been pointed out hereinabove, reference values of some kynurenines in normal population are found in the Geigy Scientific Tables. Moreover, in clinical studies performed by Applicant in epileptic patients, reference concentrations were gleaned from a group of 42 healthy adult-donors of the Israeli Blood Bank and about 20 healthy children from the Kaplan Hospital (Rehovot, Israel). These data, so obtained, correspond very well with the reference data published in Geigy Scientific Tables.

8. In paragraph 11 of the instant Office Action, the Examiner finds that claims 84 and 88 are indefinite because the presence of (e) and (f) makes the claims confusing and indefinite because these steps are not additional steps in the claim. The Examiner's rejection is respectfully traversed.

In claim 84 the added step of "determining an amount of an anti-epileptic drug in the subject" is provided and tied-in with previous steps of claim 67 by noting that diagnosis of "said medical condition is further based on said determined amount of said anti-epileptic drug."

In claim 88 the added step of "adjusting a treatment regimen of said subject

based on said diagnosing of said medical condition” is provided. It is clear that claim 88 refers to a method of the present invention specifically in assisting a health care professional in adjusting the treatment regimen of a patient by monitoring the effect a treatment, *e.g.* type and dosage of AED, has.

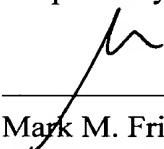
9. In paragraph 12 of the instant Office Action, the Examiner finds that claims 84-87 are confusing because they employ the terms “anti-epileptic drug” and “AED” to the same element. In order to prevent any possible confusion, Applicant has amended claims 84-87 by replacing all appearances of the term “AED” with the term “anti-epileptic drug”.

10. In paragraph 13 of the instant Office Action, the Examiner notes that there is no antecedent basis for the term “method” in claim 93. Applicant notes that this was an unintentional typographical error and has amended claim 93 by replacing the term “method” with the term “system”.

11. In paragraph 14 of the instant Office Action, the Examiner notes that claims 68-71, 73-83 and 90-92 are indefinite for being dependent from indefinite claims. Applicant believes that in light of the amendments and arguments above, the independent and dependent claims are no longer indefinite.

In light of the above, it is respectfully submitted that independent claims 67 and 89 and hence claims dependent therefrom are in condition for allowance. Prompt notice of allowance is earnestly solicited.

Respectfully Submitted,



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